Predisposition to Waldenström macroglobulinemia: the essential dynamic interplay of families and populations

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Investigation of familial clusters often provide the initial indication of a potential role for genetic or shared environmental factors in disease susceptibility. Clues provided by family studies inform the design of population studies, and data from population studies can, in turn, be applied in the familial setting. We and others have conducted studies in families and in populations to generate and explore hypotheses related to three major areas: 1) defining the pattern of malignancies that comprise the spectrum of familial WM; 2) identifying and characterizing immunoglobulin Type M monoclonal gammopathy of undetermined significance (IgM MGUS) as a precursor condition for WM; and 3) unraveling the role of genetic and shared environmental factors in WM susceptibility. Observations in family studies of Waldenström macroglobulinemia (WM) first suggested relatives of WM patients may be at increased risk for not only WM, but also other lymphoproliferative disorders (LPD) and possibly myeloid and/or solid tumors. Population studies have addressed these observationsand have provided quantitative estimates of relative risks for confirmed associations. Detailed observations in relatives of WM patients revealed a high frequency (10-20%) of asymptomatic IgM monoclonal gammopathy, including IgM MGUS. This apparent association was subsequently confirmed in population studies, and these results were shown to improve power in gene discovery efforts. Family and population studies have also confirmed a relationship with autoimmune disease in both WM patients and their relatives, with implications for predisposition research. Potential genetic markers of WM risk have been first identified in either families or populations and then investigated for their applicability in the alternate system. Interestingly, family studies were the first to suggest genetic heterogeneity and the potential interaction of genetic and shared environmental factors in WM susceptibility, with research actively continuing in this area. This paper will examine the contributions of family and population studies to the understanding of WM predisposition and identify areas of continued research interest.